PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing: 22 February 2001 (22.02.01)	
International application No.: PCT/EP00/03887	Applicant's or agent's file reference: NO 6536/WO
International filing date: 02 May 2000 (02.05.00)	Priority date: 29 April 1999 (29.04.99)
Applicant: KRATKY, Zdenek et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International preliminary Examining Authority on:

29 November 2000 (29.11.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer:

J. Zahra

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

BECKER, KURIG, STRAUS
Bavariastrasse 7
D-80336 Munich
ALLEMAGNE

Date of mailing (day/month/year)
11 juillet 2001 (11.07.01)

Applicant's or agent's file reference
NO 6536/WO

IMPORTANT NOTIFICATION

International application No.
PCT/EP00/03887

International filing date (day/month/year)
02 mai 2000 (02.05.00)

1. The following indications appeared on record concerning:

[ ] the applicant [ ] the inventor [X] the agent [ ] the common representative

Name and Address
LOCK, Graham
Avenue Nestlé 55
CH-1800 Vevey
Switzerland

State of Nationality:
State of Residence:
Telephone No.: +41 21 924 47 60
Facsimile No.: +41 21 924 28 80
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[X] the person [X] the name [X] the address [ ] the nationality [ ] the residence

Name and Address
BECKER, KURIG, STRAUS
Bavariastrasse 7
D-80336 Munich
Germany

State of Nationality:
State of Residence:
Telephone No.: +49 89 746 30 30
Facsimile No.: +49 89 746 30 311
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[X] other: former agent

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer
Lazar Joseph Panakal

Telephone No.: (41-22) 338.83.38

Form PCT/IB/306 (March 1994)

004142736

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

STRAUS, Alexander
BECKER, KURIG, STRAUS
Bavariastrasse 7
D-80336 München
ALLEMAGNE

BECKER KURIG STRAUS
BAVARIASTRASSE 7 · 80336 MÜNCHEN
30 Mai 2001
WV: ..... / LF: .....

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

	Date of mailing *(day/month/year)* 29.05.2001
Applicant's or agent's file reference 80305 WO	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/03887	02/05/2000	29/04/1999

Applicant
SOCIETE DES PRODUITS NESTLE S.A. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

30.Mon. TU 28.10.01 vol.
31.Mon. TU 28.11.01

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Hutterer, G Tel.+49 89 2399-8066

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
NO 6536/WO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 00/ 03887	02/05/2000	29/04/1999
Applicant		
SOCIETE DES PRODUITS NESTLE S.A.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

[ ] the text is approved as submitted by the applicant.

[X] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. ---

[ ] as suggested by the applicant.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

[ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 00/03887

Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

Firs line: "21" is erased.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/03887

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A23L1/29 A23L1/305 A23L1/30 A23L1/09

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A23L A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, FSTA, EPO-Internal, MEDLINE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 747 395 A (CLINTEC) 11 December 1996 (1996-12-11) page 3, line 2-5 page 3, line 36-38 page 4, line 38-40 page 5, line 45-50 claims 1,3-6,10	1-20
A	EP 0 418 593 A (MILUPA) 27 March 1991 (1991-03-27) page 4, line 25-55 page 5, line 21-29 claims; example 6	1-20

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 June 2000	23/08/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Van Moer, A

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
EP 00/03887

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 312 612 A (OTSUKA PHARMACEUTICAL) 26 April 1989 (1989-04-26) page 1, paragraph 2 -page 2, paragraph 1 page 3, paragraph 3 page 10, paragraph 2 page 16, paragraph 2 -page 17, paragraph 1 claims 1-7	1-20
A	EP 0 705 542 A (SANDOZ NUTRITION) 10 April 1996 (1996-04-10) page 1, line 1,2 page 1, line 41 -page 2, line 30 claims; example 1	1-20
A	EP 0 880 902 A (NESTLÉ PRODUKTE) 2 December 1998 (1998-12-02) cited in the application claims	1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
EP 00/03887

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
EP 747395	A	11-12-1996	US	5728678	A	17-03-1998
			CA	2177195	A	07-12-1996
			JP	9020678	A	21-01-1997
EP 418593	A	27-03-1991	AT	96621	T	15-11-1993
			DD	297304	A	09-01-1992
			DE	59003330	D	09-12-1993
			DK	418593	T	13-12-1993
			ES	2062231	T	16-12-1994
			GR	3026131	T	29-05-1998
			PT	95114	A,B	18-04-1991
			TR	24775	A	01-05-1992
EP 312612	A	26-04-1989	AU	612149	B	04-07-1991
			AU	1689388	A	02-12-1988
			CN	1031025	A	15-02-1989
			DE	3890318	T	03-05-1989
			GB	2227919	A,B	15-08-1990
			WO	8808259	A	03-11-1988
			SE	462668	B	13-08-1990
			SE	8804694	A	29-12-1988
EP 705542	A	10-04-1996	US	5719133	A	17-02-1998
			AT	161397	T	15-01-1998
			CA	2158635	A,C	22-03-1996
			DE	69501306	D	05-02-1998
			DE	69501306	T	18-06-1998
			ES	2111384	T	01-03-1998
			GR	3026072	T	29-05-1998
			HK	1005768	A	22-01-1999
			SG	33502	A	18-10-1996
			SI	705542	T	30-04-1998
			US	5719134	A	17-02-1998
EP 880902	A	02-12-1998	AU	8107798	A	30-12-1998
			WO	9853702	A	03-12-1998
			EP	0986312	A	22-03-2000

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70) 13

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
80305 WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/03887	02/05/2000	29/04/1999
International Patent Classification (IPC) or national classification and IPC A23L1/29		
Applicant SOCIETE DES PRODUITS NESTLE S.A. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
29/11/2000	29.05.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Adechy, M Telephone No. +49 89 2399 8576

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/03887

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-16	as originally filed				

Claims, No.:

1-20	as received on	07/05/2001	with letter of	06/05/2001

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 20.

because:

   ☒ the said international application, or the said claims Nos. 20 relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-20
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-20
Industrial applicability (IA)	Yes:	Claims	1-19

No: Claims

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item III

Non-establishment of opinion with regard to industrial applicability

Claim 20 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Article 35 (2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1) Reference is made to the following documents

D2: EP-A-0 418 593 (MILUPA) 27 March 1991 (1991-03-27)

2) Novelty Art. 33 (1) and (2) PCT

The subject matter of claim 1 concerns a composition for an infant formula which contains whey proteins and specific free amino acids (or an enriched milk protein). The subject matter of the said claim is not regarded as novel, since D2 (p. 2-5, examples, claims) discloses such a composition, containing the claimed amino acids, which can be in a free form, as well as the protein source of whey protein. The said document also specifies that the whey protein can be hydrolysed. In addition, it should be stressed that the said claim lacks clarity since the term "acid whey protein" is not clearly defined or delimited (see also section VIII).

Remark: The feature of a chemically treated sweet whey protein would be taken into accoun to analyse novelty if it was not an alternative and combined with an unclear feature, such as acid whey protein.

The subject matter of dependent claims 2-13 would comply with At 33 (2) PCT only in relation with an independent claim in agreement with the above mentioned article.

The subject matter of claim 14 concerns an infant formula comprising a source of protein which contains specific amino acids in a free form, and in specific amount. The subject matter of the said claim is also disclosed in D2, since the said document

describes amino acid compositions for supplementing mother milk or preparing milk formula for premature born babies and other infants. The same applies to dependent claims 15-17, for which subject matter is also disclosed in the said document.

The subject matter of claim 18 concerns a method of producing the composition of claim 1, where casein and whey proteins are blended, together with specific free amino acids. The said claim is not regarded as novel, since D2 discloses such a method, where the composition comprises the claimed components (the step of blending and homogenising also correspond to conventional manufacturing procedure). It should be noted that even if the product of claim 1 was novel, the method of claim 18 would not be regarded as novel since it does not specifies the exclusive use of, e.g., acid whey protein. Therefore, it would not show how the composition obtained would differ from that of D2 (see also section VIII).

The subject matter of claims 19 and 20 is not regarded as novel in the light of D2, since it is defined in a broad and unclear manner. The said document discloses both the use of a composition for infant formulations, as well as a method to provide infant with an improved formulation feed.

3) Inventive step Art. 33 (1) and (3) PCT

The problem to be solved in the present application consists of providing an improved composition intended for use in infant formula, having a composition close to that of mother milk and avoiding protein overload, as well as a method of manufacture of such a product, and a method of treatment of infant. The present application suggests the use of specific amino acid, in a free form and the use of whey proteins and casein. The proposed solution of the present application consists in selecting specific amino acid and decreasing the threonine content.

The closest prior art is D2 since it relates to improved infant formula. It differs from the present application in that it does not suggest the use of chemically modified whey protein source.

The subject matter of claims 1-20 does not comply with article 33 (1) - (3) PCT since their subject matter is known from D2.

4) Industrial applicability

For the assessment of the present claims 19 and 20 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII
Certain observations on the international application

1) The subject matter of claim 1 sets unclear limit to the scope of the claim, since the use of terms such as "low content", and "acid whey protein" is ambiguous. Moreover, it is not clear from the description that acid whey proteins must exclusively be used and how they would be obtained, the whole whey protein are referred to in the examples of the description, as well as in claim 18 (Art. 6 PCT).

2) The use of the term "about", or the expression "source of protein", employed in the claims renders the subject matter of the said claim unclear. A source of protein can be regarded as any composition containing proteins or a finished product itself (Art. 6 PCT).

3) The subject matter of claim 7 is defined by a result to be achieved and not in terms of technical features ("protein source having less than 10% blocked lysine"), as required by Rule 6.3 a) PCT. Therefore it is not clear how this is achieved (Art. 6 PCT).

4) The subject matter of claim 10 lacks support from the description since the combination of the various amino acids percentages, found in the said claim, was not disclosed in the description. The percentage of histidine found in the claim (1.5%) is disclosed in the description (on p. 4 l. 7) but not in connection with the percentage of the other components. The selection of the components and their proportion in the said claim, therefore lacks support (Rule 5.1 v) PCT).

5)The subject matter of claim 18 also lacks support in the description, since on page 2 l. 20-23 of the description, the presence of casein is not disclosed in the description as claimed (Rule 5.1 v) PCT). In addition, claim 18 is unclear since it is a method for manufacturing the product of claim 1, in which specific whey protein are used, and the said claim refers to the whole whey protein (Art. 6 PCT).

6) The use of the term "addressing" in claim 19 is unclear and is written twice (Art. 6 PCT).

7) The subject matter of claim 20, is unclear since the term "addressing" is not clear. In addition, it is not clear which method the claim refers to ("nutritional needs and providing healthy growth"). Finally the said claim is not defined in terms of technical features and the use of term such as "an effective amount" is ambiguous and does not set limit in scope (Art. 6 PCT and Rule 6.3 a) PCT).

8) The use of a term such as "good amino acid profile" and "an effective amount of an embodiment", found in the description on p. 2 lines 7 and 31 respectively, are ambiguous (Art. 5 PCT).

9) On p. 3 l. 17-18 of the description, the same embodiment appears twice ("about 70%:about 30%") (Art. 5 PCT).

10) The use of the unit g/gN found on, e.g., p. 5 l. 27, is not defined Art. 5 PCT).

11) The use of an expression such as "incorporated by reference" on p. 6 l. 19-20 is unclear (Art. 5 PCT).

12) According to table on, e.g., p. 11, the amount of histidine can be 0%, and the invention appears to clearly aim to supplement the composition in free amino acids, therefore the range given leaves the reader in doubt concerning the basis of the invention (Art. 5 PCT).

13) The use of an expression such as "the spirit of the invention" found on p. 16 l. 10 is unclear (Rule 9.1 iv) and Art. 5 PCT).

Claims

1. A composition for an infant formula having a protein source which has a low threonine content and which comprises all of:
   i) acid whey protein or sweet whey protein from which caseino-glyco-macropeptide has been removed; and
   ii) free arginine; and
   iii) free histidine; and
   iv) free tyrosine or free tryptophan or tryptophan rich milk protein or a mixture thereof.

2. A composition according to claim 1 wherein the protein source comprises less than about 8g threonine /16g ~~N~~ Nitrogen .

3. A composition according to any preceding claim which comprises from about 9.0 to about 10.0 w/w% of protein.

4. A composition according to any preceding claim wherein the protein source comprises casein protein.

5. A composition according to claim 4 wherein the protein source comprises about 6% to about 50% by weight of whey protein and about 20% to about 40% casein protein.

6. A composition according to any preceding claim wherein the protein source is substantially free of lactose.

7. A composition according to any preceding claim wherein the protein source has less than 10% blocked lysine.

8. A composition according to any preceding claim wherein the protein source comprises hydrolysed protein.

9. A composition according to claim 8 in which the protein source comprises about 98.5% to about 97% by weight of hydrolysed sweet whey protein and about 1.5% to about 3% by weight of arginine, tyrosine, and histidine.

10. A composition according to any preceding claim which comprises about 0.1% to about 3% by weight of arginine; about 0.2% to about 1% by weight of tryptophan or tyrosine; and about 0.1 to about 1.5% by weight of histidine.

11. A composition according to any preceding claim which comprises a lipid source, a carbohydrate source, and a protein source.

12. A composition according to claim 11 wherein the lipid source includes medium chain triglycerides.

13. A composition according to claim 11 or 12 wherein the carbohydrate source includes lactose.

14. An infant formula which comprises a composition according to any preceding claim wherein the protein source comprises up to about 0.1% by weight histidine, about 0.1% to about 0.3% by weight arginine, and about 0.3 to about 0.5% by weight tryptophan.

15. An infant formula which comprises a composition according to any one of claims 1 to 13 which wherein the protein source comprises about 0.2% to about 0.4% by weight histidine, about 1% to about 2% by weight arginine, and about 0.2% to about 0.4% by weight tryptophan.

16. An infant formula which comprises a composition according to any one of claims 1 to 13 which the protein source comprises about 1% to about 1.5% by weight histidine, about 0.6% to about 0.9% by weight arginine, and about 0.3% to about 0.5% by weight tyrosine.

17. An infant formula which comprises a composition according to any one of claims 1 to 13 which the protein source comprises about 0.2% to about 0.4% by weight histidine, about 1% to about 2% by weight arginine, and about 0.2% to about 0.4% by weight tyrosine.

18. A method of producing a composition according to any one of claims 1 to 13 which comprises the step of blending whey protein and casein protein

together with free arginine; free histidine; and tyrosine or tryptophan rich milk protein or free tryptophan or a mixture thereof and homogenising the blended mixture.

19. Use of a composition according to any one of claims 1 to 13 ~~in~~ for the manufacture of a medicament or nutritional product for addressing addressing the nutritional needs and providing healthy growth of an infant.

20. A method of addressing ~~addressing~~ the nutritional needs and providing healthy growth of an infant which comprises administering an effective amount of a composition according to any one of claims 1 to 13.

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(54) Title: COMPOSITION FOR AN INFANT FORMULA HAVING A LOW THREONINE CONTENT

(57) Abstract: A composition for an infant formula which comprises a low threonine content; a method of producing the composition; use of the composition in the manufacture of a medicament or nutritional product for addressing the nutritional needs and providing healthy growth of an infant; and a method of addressing the nutritional needs and providing healthy growth of an infant which comprises administering an effective amount of the composition. A preferred embodiment of the composition comprises all of: i) acid whey protein or sweet whey protein from which caseino-glyco-macropeptide has been removed; and ii) free arginine; and iii) free histidine; and iv) free tyrosine or free tryptophan or tryptophan rich milk protein or a mixture thereof.

Composition For An Infant Formula Having a Low Threonine Content

This invention relates to a composition for an infant formula having a low threonine content; a method of producing the composition; use of the composition in the manufacture of a medicament or nutritional product for addressing the nutritional needs and providing healthy growth of an infant; and a method of addressing the nutritional needs and providing healthy growth of an infant which comprises administering an effective amount of the composition.

Within the context of this application the word "comprises" is taken to mean "includes, among other things" and it is not intended to mean "consists of only".

Mother's milk is recommended for all infants. However, in some cases mother's milk is not available and infant formulae must be used. Normal, full-term infants are usually fed cow's-milk-based formulas. These formulas contain a mixture of casein and whey as protein sources and they provide nutrition for infants, however they do not provide a protein concentration and an amino acid profile equivalent to that of mother's milk. In addition these standard formulae are not suitable for pre-term infants and those having adverse reactions to protein in cow's milk formula or to lactose.

An alternatives to cow's milk formula is soy formula; particularly for infants who are lactose intolerant. However, soy is not as good a protein source as cow's milk. Also, infants do not absorb some minerals, such as calcium, as efficiently from soy formulae.

A further alternative formula is based on hydrolysed protein. These formulas are hypoallergenic and have a decreased likelihood of an allergic reaction.

Ideally, to be as close as possible to human milk, the protein in infant formulae may be derived from both whey and casein in an appropriate ratio. However, a problem with conventional formulae having these proteins is that they have a high protein concentration to ensure that the infant gets the necessary amount of all essential amino acids. The protein concentration is higher than the concentration normally found in human milk and it may not be beneficial for an

infant because an infant's metabolism is susceptible to overloading with nitrogen from its protein intake.

To address this problem, formulae having improved amino acid profiles have been suggested, for example those having hydrolysed whey proteins. However, until now there has not been a composition having a protein concentration equivalent to the concentration in human milk and a good amino acid profile.

The present invention addresses the problems set out above.

Accordingly, the invention provides a composition for an infant formula having a low threonine content which comprises all of:

i) acid whey protein or sweet whey protein from which caseino-glyco-macropeptide has been removed; and
ii) free arginine; and
iii) free histidine; and
iv) free tyrosine or tryptophan rich milk protein or free tryptophan or a mixture thereof.

In a second aspect the invention provides a method of producing the composition which comprises the step of blending whey protein together with free arginine; free histidine; and free tyrosine or tryptophan rich milk protein, free tryptophan or a mixture thereof and homogenising the blended mixture.

In a third aspect the invention provides use of an embodiment of the composition in the manufacture of a medicament or nutritional product for addressing the nutritional needs and providing healthy growth of an infant.

In a forth aspect the invention provides a method of addressing the nutritional needs and providing healthy growth of an infant which comprises administering an effective amount of an embodiment of the composition.

Preferably the protein source has a threonine content of less than about 8g/16gN, more preferably it is less than about 6g/16gN.

Preferably an embodiment of the composition comprises from about 9.0 to about 10.0 w/w% of protein, more preferably about 9.5% w/w%. This corresponds to about 1.8g protein /100kcal. This provides the advantage of a lower protein concentration relative to known formulae. An advantage provided by this concentration of protein is that it is equivalent to the amount of protein generally present in human milk and it corresponds to the lower limit tolerated by codex alimentarius.

Preferably an embodiment of the composition comprises about 6% to about 50% by weight of whey protein, more preferably about 20% to 40% whey protein, most preferably 30% whey protein.

Preferably the composition also comprises casein protein. An advantage provided by casein is that it has the ability to form curd which enhances the feeling of satiety. Preferably it comprises from about 20% to about 40% casein protein, more preferably about 30%. Preferably, the ratio of whey protein to casein protein is about 60%:about 40% to about 70%:about 30%, most preferably it is about 70%:about 30%.

Preferably the whey protein is acid whey protein or sweet whey protein. In general, acid whey protein is preferred from a nutritional point of view since it has a lower threonine content and this is closer to that of human milk.

Preferably, the sweet whey protein is sweet whey protein from which caseino-glyco-macropeptide has been removed. This provides the advantage of a reduced threonine content and an increased tryptophan content as compared to normal sweet whey and is therefore suitable as a protein source for infants.

Preferably, the whey protein is substantially free of lactose. This has the advantage that the infant formula has reduced levels of lysine blockage. Preferably, the level of lysine blockage is less than 10%.

Preferably an embodiment of the composition comprises protein which is non-hydrolysed. In alternative embodiments it is hydrolysed.

Preferably an embodiment of the composition comprises up to about 4% by weight of arginine; up to about 4% tyrosine or tryptophan; up to about 4% histidine. More preferably an embodiment of the composition comprises about 0.1% to about 3% by weight of arginine; about 0.2% to about 1% tyrosine or tryptophan; about 0.1% to about 2% histidine. More preferably an embodiment of the composition comprises about 0.1% to about 2% by weight of arginine; about 0.2% to about 0.5% tyrosine or tryptophan; about 0.1% to about 1.5% histidine. Suprisingly, it has been found that by supplementing with the free amino acids arginine, tyrosine, and histidine, the protein source has an amino acid profile which is close to that of human milk. This provides the advantage of mimicking the nutritional benefits of natural human milk for addressing the nutritional needs and providing healthy growth of an infant.

Preferably the concentration of tryptophan in the composition is at least about 135mg/g and the concentration of threonine in the composition is less than about 350mg/g. Preferably the threonine concentration corresponds to about 4.9 g per 100g protein to about 5.1g per 100g protein.

Preferably, tryptophan rich milk protein has a level of about 5% or more of amino acids as tryptophan. More preferably it is about 10% or more.

Preferably the free amino acids are in free base form.

Preferably an embodiment of the composition comprises a lipid source, a carbohydrate source, and a protein source. This provides the advantage that the composition is as close as possible in content to mothers milk.

The lipid source may contain medium chain triglycerides.

The carbohydrate source may include lactose. The lactose may be the sole source of carbohydrates.

In one embodiment the composition is suitable for a pre-term infant formula and comprises up to about 0.1% by weight histidine, about 0.1% to about 0.3% by weight arginine, and about 0.3 to about 0.5% by weight tryptophan.

In an alternative embodiment the composition is suitable for a full-term, hypoallergenic infant formula in which the protein source preferably comprises about 0.2% to about 0.4% by weight histidine, about 1% to about 2% by weight arginine, and about 0.2% to about 0.4% by weight tryptophan.

In an embodiment which comprises hydrolysed protein, the protein source preferably comprises about 98.5% to about 97% by weight of hydrolysed sweet whey and about 1.5% to about 3% by weight of arginine, tyrosine, and histidine.

An embodiment which comprises hydrolysed protein may be suitable for a pre-term infant formula in which the protein source comprises about 1% to about 1.5% by weight histidine, about 0.6% to about 0.9% by weight arginine, and about 0.3% to about 0.5% by weight tyrosine. In this case, the lipid source may include medium chain triglycerides.

An alternative embodiment which comprises hydrolysed protein may be suitable for a full-term, hypoallergenic infant formula in which the protein source comprises about 0.2% to about 0.4% by weight histidine, about 1% to about 2% by weight arginine, and about 0.2% to about 0.4% by weight tyrosine. The carbohydrate source may include lactose which may be the sole source of carbohydrates.

In an embodiment the invention provides a pre-term infant formula which comprises a lipid source which includes medium chain triglycerides, a carbohydrate source, and a protein source which contains a hydrolysed or non-hydrolysed sweet whey fraction having a level of lysine blockage less than 10%, the protein source having a threonine content of less than about 6 g/16gN.

In a further embodiment, the invention provides a full-term, hypoallergenic infant formula which comprises a lipid source, a carbohydrate source which includes lactose, and a protein source which contains a hydrolysed or non-hydrolysed sweet whey fraction having a level of lysine blockage less than 10%, the protein source having a threonine content of less than about 6 g/16gN.

Embodiments of the invention are now described by way of example.

The invention provides a composition for an infant formula which comprises arginine, tryptophan or tyrosine, histidine and a sweet whey fraction from which caseino-glyco-macropeptide has been removed. The infant formula may be used for pre-term or full-term infants.

An embodiment having hydrolysed protein may be used for pre-term infants or infants susceptible to allergic reactions.

The sweet whey used in the protein source may be obtained from cheese making, particularly the sweet whey obtained after the coagulation of casein by rennet. The sweet whey may then be processed as desired. For example, the sweet whey may be treated to remove minerals (cations, anions), lactose, or any of these substances. The sweet whey may be concentrated as desired. Suitable sweet whey sources are commercially available. It is particularly preferred that the sweet whey is substantially lactose-free.

The sweet whey is then treated to remove caseino-glyco-macropeptide. This may be accomplished by any suitable process. One suitable process is described in European patent application 0880902, the disclosure of which is incorporated by reference. In this process, the pH of the sweet whey is adjusted to 1 to 4.3, if necessary. The sweet whey is then contacted with a weakly anionic resin which is predominantly alkaline until the pH of the sweet whey stabilises at about 4.5 to 5.5. The sweet whey fraction from which the caseino-glyco-macropeptide has been removed, is then collected.

In an embodiment of the composition the whey protein is non-hydrolysed. In an alternative embodiment, the sweet whey fraction is hydrolysed to prevent allergic reactions in infants at risk and to make the protein easier to digest. The hydrolysis process may be carried out as desired and as is known in the art. In general, the whey protein hydrolysate is prepared by enzymatically hydrolysing the sweet whey fraction in one or more steps. For example, for an extensively hydrolysed protein, the sweet whey proteins may be subjected to triple hydrolysis using, for example, Alcalase 2.4L (EC 940459), then Neutrase 0.5L (obtainable from Novo Nordisk Ferment AG) and then pancreatin at 55°C. Alternatively, for a less hydrolysed protein, the sweet whey may be subjected to double hydrolysis using, for example, NOVOZYMES and then pancreatin.

If the sweet whey fraction used is substantially lactose free, it is found that the protein is subjected to much less lysine blockage during the hydrolysis process. This enables the extent of lysine blockage to be reduced from about 15% by weight of total lysine to less than about 10% by weight of lysine; for example about 7% by weight of lysine. This greatly improves the nutritional quality of the protein source.

The free amino acids L-arginine, L-tryptophan or L-tyrosine, and L-histidine are included in the protein source. Preferably, they are in the form of free amino acids and make up about 0.2% to about 3% by weight of the protein source. For example, the free amino acids may make up about 2% to about 2.6% by weight of the protein source.

In particular, for pre-term formulas, histidine preferably provides about 1% to about 1.5% by weight, arginine preferably provides about 0.6% to about 0.9% by weight, and tryptophan or tyrosine preferably provides about 0.3% to about 0.5% by weight, of the protein source. For hypoallergenic formulas, histidine preferably provides about 0.2% to about 0.4% by weight, arginine preferably provides about 1% to about 2% by weight, and tryptophan or tyrosine preferably provides about 0.2% to about 0.4% by weight, of the protein source.

The protein source may include other free amino acids as desired.

The carbohydrate source in the infant formula can be carbohydrate suitable for use in infant formulas. Preferred carbohydrate sources are selected from the group which comprises sucrose, maltodextrin, maltose, lactose, corn syrup, corn syrup solids, rice syrup solids, rice starch, and the like. Preferably, the carbohydrate source includes lactose and maltodextrin. The lactose is preferably free of any allergens. For full term formulas, the carbohydrate source is preferably lactose.

The lipid source may be any lipid or fat which is suitable for use in infant formulas. Preferred lipid sources include milk fat, safflower oil, egg yolk lipid, canola oil, olive oil, coconut oil, palm oil, palm kernel oil, palm olein, soybean oil, sunflower oil, fish oil, and microbial fermentation oil containing long-chain,

polyunsaturated fatty acids. These oils may be in the form of high oleic forms such as high oleic sunflower oil and high oleic safflower oil. The lipid source may also be in the form of fractions derived from these oils such as palm olein, medium chain triglycerides (MCT), and esters of fatty acids such as arachidonic acid, linoleic acid, palmitic acid, stearic acid, docosahexaeonic acid, linolenic acid, oleic acid, lauric acid, capric acid, caprylic acid, caproic acid, and the like.

For pre-term formulas, the lipid source preferably contains medium chain triglycerides; for example in an amount of about 15% to about 35% by weight of the lipid source.

The lipid source preferably has a ratio of n-6 to n-3 fatty acids of about 5:1 to about 15:1; for example about 8:1 to about 10:1.

The infant formula may further comprise ingredients which are designed to meet the nutritional needs of a human infant. In particular, it is preferred that the infant formula is "nutritionally complete"; that is it contains adequate nutrients to sustain healthy human life for extended periods.

The amount of protein per 100 kcal of formula is typically about 1.8g to about 4.5 g; for example about 1.8 g to about 4 g. For full term hypoallergenic formulas, the amount may be about 1.8 g/100 kcal to about 2.5 g/100 kcal. In order to reduce protein loading, the amount is preferably less than about 2 g/100 kcal. For pre-term formulas, the amount may be about 1.8 g/100 kcal to about 4 g/100 kcal.

The amount of lipid source per 100 kcal of formula may be about 3.3 g to about 6.5 g; for example about 4.4 g to about 6.5g. The amount of carbohydrate source per 100 kcal of total formula is typically about 7 g to about 14 g.

When in nutritionally complete form, the infant formula contains all vitamins and minerals understood to be essential in the daily diet and in nutritionally significant amounts. Minimum requirements have been established for certain vitamins and minerals. Examples of minerals, vitamins and other nutrients optionally present in the infant formula include vitamin A, vitamin B_1, vitamin B_2, vitamin B_6, vitamin B_{12}, vitamin E, vitamin K, vitamin C, vitamin D, folic

acid, inositol, niacin, biotin, pantothenic acid, choline, calcium, phosphorous, iodine, iron, magnesium, copper, zinc, manganese, chloride, potassium, sodium, selenium, chromium, molybdenum, taurine, and L-carnitine. Minerals are usually added in salt form. The presence and amounts of specific minerals and other vitamins will vary depending on the intended infant population.

If necessary, the infant formula may contain emulsifiers and stabilisers such as soy lecithin, citric acid esters of mono- and di-glycerides, and the like. This is especially the case if the formula is provided in liquid form.

The infant formula may optionally contain other substances which may have a beneficial effect such as fibres, lactoferrin, nucleotides, nucleosides, and the like.

The infant formula may be prepared in any suitable manner. For example, for an infant formula may be prepared by blending together the protein source, the carbohydrate source, and the fat source in appropriate proportions. If used, the emulsifiers may be included in the blend. The vitamins and minerals may be added at this point but are usually added later to avoid thermal degradation. Any lipophilic vitamins, emulsifiers and the like may be dissolved into the fat source prior to blending. Water, preferably water which has been subjected to reverse osmosis, may then be mixed in to form a liquid mixture.

The liquid mixture may then be thermally treated to reduce bacterial loads. For example, the liquid mixture may be rapidly heated to a temperature in the range of about 80°C to about 110°C for about 5 seconds to about 5 minutes. This may be carried out by steam injection or by heat exchanger; for example a plate heat exchanger.

The liquid mixture may then be cooled to about 60°C to about 85°C; for example by flash cooling. The liquid mixture may then be homogenised; for example in two stages at about 7 MPa to about 40 MPa in the first stage and about 2 MPa to about 14 MPa in the second stage. The homogenised mixture may then be further cooled to add any heat sensitive components; such as vitamins and minerals. The pH and solids content of the homogenised mixture is conveniently standardised at this point.

If it is desired to produce a powdered infant formula, the homogenised mixture is transferred to a suitable drying apparatus such as a spray drier or freeze drier and converted to powder. The powder should have a moisture content of less than about 5% by weight.

If it is desired to produce a liquid infant formula, the homogenised mixture is filled into suitable containers; preferably aseptically. However, the liquid infant formula may also be retorted in the container. Suitable apparatus for carrying out filling of this nature is commercially available. The liquid infant formula may be in the form of a ready to feed formula having a solids content of about 10 to about 14% by weight or may be in the form of a concentrate; usually of solids content of about 20 to about 26% by weight.

Specific examples of the invention are now described for illustration.

Example 1

a) A sweet whey protein concentrate is dissolved in deionised water and the pH is adjusted to 4.25 by contacting the solution with a cation exchange resin (IMAC HP 1100 E, Rohm and Haas). The solution is treated with a weakly anionic resin (IMAC HP 661, Rohm & Haas, which has been regenerated in OH^- form) for about 6 hours at 8°C. Once the pH reaches about 5.25 and does not change, the solution is recovered. Over 85% of the caseino-glyco-macropeptide originally present has been removed from the solution.

b) The solution of step a) is standardised in demineralised water at 55°C. The solution is then heated to 75°C for 20 seconds. The pH of the solution is adjusted to 7.5 by the addition of $Ca(OH)_2$ and a solution of NaOH and KOH.

The reaction mixture is then subjected to microfiltration and ultrafiltration and then dried by lyophilisation and packaged into metal cans. The protein has low levels of lysine blockage with 6.9% blocked lysine and 9% reactive lysine.

c) The protein of step b) is combined with 0.72% by weight L-arginine, 0.44% by weight of L-tryptophan, and 1.38% by weight of L-histidine. The mixture is formulated into a powdered infant formula. The infant formula has the following composition:

Component	Amount
Milk SNF	8-10%
Whey protein	6-50%
Alpha-lactalbumin rich whey protein source	0-2%
Arginine	0.1-0.3%
Histidine	0-0.1%
Fat	25-30%
Lactose	10-40%
Vitamins and minerals	To meet regulations

The composition has a protein concentration of 9.5 w/w% or 1.8g protein /100kcal.

Example 2

Step a) is carried out as in Example 1.

b) The solution of step a) is standardised in demineralised water at 55°C. The solution is then heated to 75°C for 20 seconds. The pH of the solution is adjusted to 7.5 by the addition of $Ca(OH)_2$ and a solution of NaOH and KOH. The protein is then hydrolysed using the NOVOZYME enzyme (obtainable from Novo Nordisk Ferment AG). The hydrolysis reaction is continued for 4 hours at 55°C.

An amount of pancreatin is added and the protein is further hydrolysed for 8 hours at 55°C and at a pH of 7.0. The enzymes are then inactivated by heating the reaction mixture to 90°C and holding the mixture at this temperature for about 5 minutes. The reaction mixture is then cooled to 5°C.

The reaction mixture is then subjected to microfiltration and ultrafiltration. The hydrolysed protein is then dried by lyophilisation and packaged into metal cans. The hydrolysed protein has low levels of lysine blockage with 6.9% blocked lysine and 9% reactive lysine.

c) The hydrolysed protein of step b) is combined with 0.72% by weight L-arginine, 0.44% by weight of L-tyrosine, and 1.38% by weight of L-histidine. The mixture is formulated into a powdered infant formula. The infant formula has the following composition:

Component	Amount per 100 kcal
Protein	3.6 g
Hydrolysed whey	3.5 g
Free amino acids	0.1 g
Lipids	5.2 g
Medium chain triglycerides	
High oleic sunflower oil	
Soya bean oil	
Palm olein	
Fish oil	
Egg phospholipids	
Carbohydrates	9.9 g
Lactose	2.0 g
Maltodextrin	7.9 g
Vitamins and minerals	To meet regulations

The infant formula is suitable for pre-term infants and has the following amino acid profile:-

Amino Acids	**gAA/16gN**
Aspartic Acid	11.64
Threonine	5.69
Serine	4.79
Glutamic Acid	16.69
Proline	4.90
Glycine	2.16
Alanine	5.37

Cystine	2.69
Valine	5.37
Methionine	2.26
Isoleucine	5.32
Leucine	12.53
Tyrosine	3.42
Phenylalanine	3.95
Lysine	9.58
Histidine	3.37
Arginine	3.42
Tryptophan	2.16

Example 3

a) The solution of step a) of example 1 is standardised in demineralised water at 55°C. The pH is increased from 6.6 to 7.9 by addition of a 20% (weight/volume) aqueous dispersion of $Ca(OH)_2$. The pH is then regulated at 7.3 by compensation with a 2N aqueous solution of KOH.

Pancreatic trypsin is added to initiate hydrolysis and the reaction is continued for 4 hours at 50° C. The hydrolysate is then heated to 90°C by injection of steam and is kept at this temperature for 5 minutes. After cooling to 55° C, the pH is readjusted to 7.3 by automatic compensation with a 2N aqueous solution of KOH. Porcine trypsin is then introduced to initiate second hydrolysis which is continued for 2 hours with automatic compensation of the pH. The hydrolysate is then heat-treated for 10 minutes at 90°C, rapidly cooled and then dried by freeze-drying.

The hydrolysed protein has low levels of lysine blockage. The hydrolysed protein has low levels of lysine blockage with 6.9% blocked lysine and 9% reactive lysine.

b) The hydrolysed protein of step a) is combined with 1.52% by weight L-arginine, 0.3% by weight of L-tyrosine, and 0.3% by weight of L-histidine. The infant formula has the following composition:

Component	Amount per 100 kcal

Protein	1.9 g
Hydrolysed whey	1.86 g
Free amino acids	0.04 g
Lipids	5.1 g
Palm olein	
Coconut oil	
Sunflower oil	
Canola oil	
Egg phospholipids	
Carbohydrates	11.6 g
Lactose	11.6 g
Vitamins and minerals	To meet regulations

The infant formula is suitable for full term, hypoallergenic infants and has a balanced amino acid profile.

Example 4

To compensate for the lesser quality of bovine milk proteins, infant formulae contain more protein than human milk. By improving the quality of the protein it is possible to use less protein. It has now been found that a formula containing modified sweet whey (having caseino-glyco-macropeptide removed) with about 1.83g protein /100kcal results in similar nitrogen retention as a conventional whey-enriched formula with 2.24g protein /100kcal. This has been tested by performing metabolic balance studies with 8 normal infants (2 girls, 6 boys, aged between 39 and 139 days) in a balanced cross-over design. A metabolic balance study (72 hours) was performed with each formula after a washout period of 11 days. The formula having 1.83g protein /100kcal contained modified sweet whey and casein and casein in a ratio of 70:30. The formula having 2.24 g protein /100kcal contained demineralised whey and casein in a ratio of 60:40. In other respects the compositions were similar to commercially available infant formulae.

Results

	Nitrogen (mg/kg/d)

	intake	Ur. Excr.	Fec. Excr.	Retent.
Formula having 1.83g protein /100kcal	349±83	194±21	37±15	117±62
Formula having 2.24 g protein /100kcal	284±54	136±25	31±10	117±63

The data show that adjustment of urinary nitrogen excretion enabled infants to maintain nitrogen retention at identical levels in spite of a substantial difference in intake. Absorption and retention of minerals and fat were similar with both formulae. It was concluded that a modified whey formula with protein-energy ratio 1.83g/100kcal leads to adequate nitrogen and mineral retention in normal infants. Lower urinary nitrogen excretion indicates reduced metabolic load.

Example 5

Commercially available infant formulae contain more protein (>2g/100kcal) than human milk; it is well established that plasma amino acids (AA) of formulae-fed infants deviate from breastfed infants. It has now been found that infants fed two formulae varying in amount and composition of protein (modified whey; 1.83g protein /100kcal; F-1.8 & F-1.8LCP) have AA closer to breast fed infants than infants a whey enriched formula (2.24g protein/100kcal; F-2.2). The 3 formulae were exclusively fed between 6 and 122 days of age. Blood was collected at 30, 61 and 122 days of age. Formula intake and the intervals between last feeding and blood sampling were recorded. AA (ion exchange; tryptophan: HPLC) were measured in plasma of breastfed infants (n=19) and infants fed formula F-1.8 (n=23), F-1.8LCP (n=20), F-2.2 (n=13). Statistical analysis was carried out by Kruskal-Wallis and Mann-Whitney tests. Levels of threonine, the branched chain AA, phenylalanine and lysine in the group fed F-2.2 were significantly higher than in the breastfed group. In the groups fed F-1.8 and F-1.8LCP threonine was close to the breastfed group and the branched-chain AA were not different from the breastfed group. Glycine concentrations win the groups F-1.8 and F-1.8LCP were higher than in the breastfed group. Since the time intervals between feeding and blood sampling did not differ among the groups, the dependence of citruline on protein load with formula (F-2.2, F-1.8, F1.8LCP)

was found to be significant. The higher plasma urea values in the group F-2.2 are therefore due to increased synthesis and not decreased urinary urea excretion. It can be concluded that feeding modified whey formula with 1.8g protein/ 100kcal results in plasma amino acids at 30, 61 and 122 days of age which are close to breastfed infants.

It should be understood that various changes and modifications to the presently preferred embodiments described herein will be apparent to those skilled in the art. Such changes and modifications can be made without departing from the spirit and scope of the present invention and without diminishing its attendant advantages. It is therefore intended that such changes and modifications be covered by the appended claims.

Claims

1. A composition for an infant formula having a protein source which has a low threonine content and which comprises all of:
   i) acid whey protein or sweet whey protein from which caseino-glyco-macropeptide has been removed; and
   ii) free arginine; and
   iii) free histidine; and
   iv) free tyrosine or free tryptophan or tryptophan rich milk protein or a mixture thereof.

2. A composition according to claim 1 wherein the protein source comprises less than about 8g threonine /16gN.

3. A composition according to any preceding claim which comprises from about 9.0 to about 10.0 w/w% of protein.

4. A composition according to any preceding claim wherein the protein source comprises casein protein.

5. A composition according to claim 4 wherein the protein source comprises about 6% to about 50% by weight of whey protein and about 20% to about 40% casein protein.

6. A composition according to any preceding claim wherein the protein source is substantially free of lactose.

7. A composition according to any preceding claim wherein the protein source has less than 10% blocked lysine.

8. A composition according to any preceding claim wherein the protein source comprises hydrolysed protein.

9. A composition according to claim 8 in which the protein source comprises about 98.5% to about 97% by weight of hydrolysed sweet whey protein and about 1.5% to about 3% by weight of arginine, tyrosine, and histidine.

10. A composition according to any preceding claim which comprises about 0.1% to about 3% by weight of arginine; about 0.2% to about 1% by weight of tryptophan or tyrosine; and about 0.1 to about 1.5% by weight of histidine.

11. A composition according to any preceding claim which comprises a lipid source, a carbohydrate source, and a protein source.

12. A composition according to claim 11 wherein the lipid source includes medium chain triglycerides.

13. A composition according to claim 11 or 12 wherein the carbohydrate source includes lactose.

14. An infant formula which comprises a composition according to any preceding claim wherein the protein source comprises up to about 0.1% by weight histidine, about 0.1% to about 0.3% by weight arginine, and about 0.3 to about 0.5% by weight tryptophan.

15. An infant formula which comprises a composition according to any one of claims 1 to 13 which wherein the protein source comprises about 0.2% to about 0.4% by weight histidine, about 1% to about 2% by weight arginine, and about 0.2% to about 0.4% by weight tryptophan.

16. An infant formula which comprises a composition according to any one of claims 1 to 13 which the protein source comprises about 1% to about 1.5% by weight histidine, about 0.6% to about 0.9% by weight arginine, and about 0.3% to about 0.5% by weight tyrosine.

17. An infant formula which comprises a composition according to any one of claims 1 to 13 which the protein source comprises about 0.2% to about 0.4% by weight histidine, about 1% to about 2% by weight arginine, and about 0.2% to about 0.4% by weight tyrosine.

18. A method of producing a composition according to any one of claims 1 to 13 which comprises the step of blending whey protein and casein protein

together with free arginine; free histidine; and tyrosine or tryptophan rich milk protein or free tryptophan or a mixture thereof and homogenising the blended mixture.

19. Use of a composition according to any one of claims 1 to 13 in the manufacture of a medicament or nutritional product for addressing addressing the nutritional needs and providing healthy growth of an infant.

20. A method of addressing addressing the nutritional needs and providing healthy growth of an infant which comprises administering an effective amount of a composition according to any one of claims 1 to 13.